Diffusion anisotropy in WM depends on myelin content in a diffusion time-dependent manner: evidence from high b value q-space diffusion MR of myelin deficient rat spinal cord

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Synopsis

The relative importance of myelin in the determining diffusion anisotropy of water in white matter (WM) remains elusive. To address this problem, high b value q-space diffusion MRS and MRI were performed on myelin deficient (*md*) and age-matched control spinal cords at different diffusion times and gradient pulse durations. Although differences in the diffusion characteristics between the two groups was observed at all diffusion times, diffusion anisotropy was apparent only at relatively long diffusion times. The possible implications of these results on the use of diffusion anisotropy for detecting WM abnormalities is briefly discussed.

Introduction

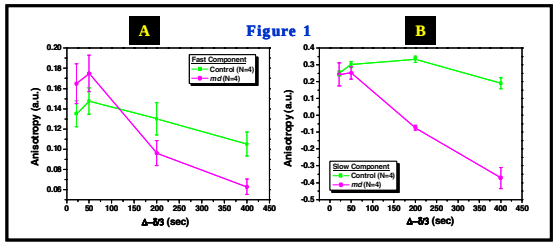
Water diffusion anisotropy is an important contrast mechanism in MRI of the central nervous system (CNS) (1). Indeed, diffusion tensor imaging (DTI) is currently heavily used for fiber tracking and detecting CNS pathologies (2). However, the relative importance of the myelin sheath in determining the diffusion anisotropy of water in white matter (WM) is still elusive. To address this problem, we used high b value q-space diffusion MRI to study water diffusion in excised spinal cords of myelin deficient (*md*) and age-matched control rats. In a preliminary study, we surprisingly found that, although diffusion characteristics were different for the two groups under the experimental conditions used, the difference in the diffusion anisotropy was found to be statistically insignificant between these groups. To further explore whether the use of different experimental conditions will have an effect on these surprising observations, we measured the anisotropy maps, obtained from high b value q-space diffusion MRS and MRI of the spinal cords of these two groups by varying different diffusion parameters. Both the effect of the diffusion gradient pulse duration (δ) and diffusion time (Δ–δ/3) was evaluated.

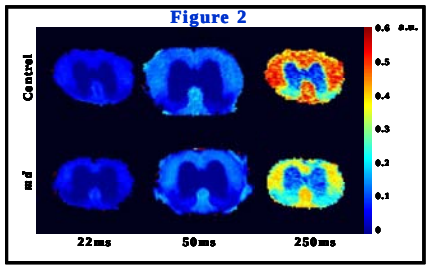
Methods

The study was performed on twenty-one day old *md* (N=10) and control (N=10) rat spinal cords fixed in 4% paraformaldehyde solution. Four of each rat group were used in the exploration of the effect of diffusion time and pulse duration. MRI/MRS experiments were performed on an 8.4T NMR spectrometer (Bruker, Germany) equipped with a micro5 gradient probe capable of producing pulse gradients of up to 190 gauss/cm in each of the three directions. MRS diffusion experiments of water were performed using the STE diffusion sequence with the following parameters: TR=3000ms, TE=40ms, and δ=4.5ms. The pulse gradient strength was incremented from 0 to 160 gauss cm^{-1} and, in each experiment, 24 b-values were acquired. In the measurements of the diffusion time effect, the diffusion times (Δ–δ/3) were 6, 8, 10, 12, 22, 50, 200 and 400ms. In the measurements of the diffusion gradient pulse duration effect, the δ and G_{max} were set to 2, 4, 8, 16 and 32ms and 160, 80, 40, 20 and 10gauss/cm, respectively with a diffusion time (Δ–δ/3) of 50ms. Diffusion was measured perpendicular (x) and parallel (z) to the long axis of the spine. In the MRI protocol, we acquired multislice, transverse T_1-weighted images (TR/TE=700/15ms) and diffusion-weighted data with a slice thickness of 1.35mm and an FOV of 8.5x8.5mm. Diffusion-weighted data were acquired using the stimulated-echo diffusion imaging sequence with the following parameters: TR/TE=2000/30ms, δ=2ms, G_{max}=50gauss/cm resulting in a b_{max} and q_{max} of $3.53x10^5$ s/cm^2 and $426cm^{-1}$, respectively. The diffusion times (Δ) were 22, 50 and 250ms. Diffusion was measured perpendicular and parallel to the long axis of the spine. In each experiment, 16 b-values were acquired and the displacement, probability and anisotropy maps were calculated as previously described (3-4). The temperature in the magnet was maintained at 25 ± 0.1^0C throughout the MRS/MRI experiments.

Results

First we examined the effect of diffusion time (Δ–δ/3) and gradient duration (δ) on WM anisotropy in *md* and their age-matched control spinal cords by diffusion MRS measurements. The water signal decays of the age-matched control and *md* rat spinal cords at sufficient long diffusion times revealed non-mono-exponential signal decays and two water diffusing components were extracted. While the diffusion gradient duration had no effect on the differences between the anisotropy of the two groups, the diffusion time had a dramatic effect. At short diffusion times ((Δ–δ/ 3)≤12ms) we found mono-exponential signal decay for the two groups, but no differences in the diffusion anisotropy was found. However, at long diffusion times ((Δ–δ/3)>22ms) two diffusing components of water were extracted and differences between the anisotropy of the fast and slow components of the two rat groups were observed. Figures 1A and 1B show the anisotropy ((Z-X)/(Z+X)) index of the fast and slow diffusing components of water in the age-matched control and *md* spinal cords as a function of the diffusion time (Δ–δ/3), respectively. At diffusion times higher than 50ms, the anisotropy of the fast and slow diffusing components of water in the *md* spinal cords are significantly lower than those of the age-matched controls. The conclusion from the MRS measurements led us to believe that the use of longer diffusion times in the diffusion MRI experiments will result in better discrimination between the anisotropies of the age-matched control and *md* spinal cords. Therefore, we measured the anisotropy maps of the spinal cords of these two rat groups at three different diffusion times i.e., 22, 50 and 250ms as shown in Figure 2. Indeed, only at a diffusion time of 250ms did we find statistically significant differences ($p<0.01$) between the anisotropy values of the *md* and age-matched control spinal cords. In contrast to the anisotropy measurements, we found significant differences between the q-space parameters (displacement and probability for zero displacement) of the age-matched control and *md* spinal cords at all diffusion times measured.





Discussion

In this study we examined the effect of the lack of myelination on the diffusion characteristic and diffusion anisotropy of water in WM as extracted from high b value q-space diffusion MRS and MRI in rat spinal cords. We tested the effect of diffusion parameters on the observed anisotropy. The spectroscopic measurements showed that the diffusion time has a dramatic effect on the difference between the water anisotropy of the WM of the two groups. While q-space parameters were different for the two groups at all diffusion times, diffusion anisotropy was different only at long diffusion times. Our study shows that myelin has an effect on the WM anisotropy, but this effect depends on the diffusion time used. Therefore, we believe that better characterization of demyelination diseases, such as multiple sclerosis, by diffusion anisotropy would require longer diffusion times (>100ms). These results suggest that there are cases in which computing the diffusion anisotropy reduces the delectability of the pathology.

References

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